Kaohsiung Journal of Medical Sciences (2016) 32, 317–322

Available online at www.sciencedirect.com

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ORIGINAL ARTICLE

Methotrexate treatment in progressive tubal ectopic pregnancies and hCG-related clinicosurgical implications

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Received 15 February 2016; accepted 28 April 2016
Available online 31 May 2016

KEYWORDS
β-hCG;
Ectopic pregnancy;
Failure;
Methotrexate;
Treatment

Abstract Our aim was to evaluate the relationship between the success of methotrexate treatment and β-hCG levels in progressive tubal ectopic pregnancies. We defined a retrospective cohort of 394 progressive tubal ectopic pregnancy patients treated with methotrexate. A single-dose methotrexate protocol using 50 mg/m^2 was administered to patients with progressive tubal ectopic pregnancy. Surgery was performed in patients who exhibited signs of acute abdomen due to tubal rupture. Of 394 patients that received methotrexate treatment, 335 (84.6%) responded to medical treatment, while the remaining 59 (15.36%) underwent surgery due to treatment failure. β-hCG levels in the failure group were significantly higher as compared with the success group at Day 1, Day 4, and Day 7 (2116 ± 3157 vs. 4178 ± 3422, 2062 ± 3551 vs. 4935 ± 4103, and 1532 ± 3007 vs. 3900 ± 4783, respectively). The receiver operating characteristics curve for β-hCG levels at Day 1 was 0.738, with a cutoff value of 1418 mIU/mL, while sensitivity and specificity values reached the optimum for treatment success (83.1% and 59.4%, respectively). Medical treatment with methotrexate achieved an 85.02% success rate for the treatment of progressive tubal ectopic pregnancy, while success rates for medical treatment decreased significantly when initial β-hCG levels were >1418 mIU/mL.

Conflicts of interest: All authors declare no conflicts of interest.

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http://dx.doi.org/10.1016/j.kjms.2016.05.004

Introduction

Ectopic pregnancy (EP) occurs in ~1–2% of all pregnancies [1]. Assisted reproductive techniques, a history of pelvic inflammatory disease, tubal surgery, and a history of EP are established risk factors for EP [2]. Patients showing a decline or plateau in β-hCG levels are managed expectantly. In hemodynamically stable patients, treatment during this period involves medical therapy if the β-hCG levels plateau or increase. In hemodynamically unstable patients with signs of acute abdomen or rupture of EP, the only treatment choice is surgery [3].

Medical treatment includes the use of methotrexate, which is currently used worldwide and is the most efficient agent. Methotrexate is preferred, because it has few side effects and high efficiency. Various administration protocols are used in clinical practice involving single-, two-, and fixed-dose regimens [3]. Monitoring serial β-hCG levels and the clinical findings associated with tubal rupture, such as hemodynamic instability and severe pain, are helpful in evaluating the efficacy of medical therapy. Serial β-hCG monitoring can also be used to differentiate spontaneously resorbing EP from progressive EP. Single-dose methotrexate is the most common treatment protocol, with the main purpose being achieving maximum success from administering the lowest dose possible with minimal side effects.

This study investigated the success of methotrexate therapy and factors affecting treatment success in patients with progressive tubal ectopic pregnancy (PTEP).

Methods

This retrospective study was conducted at Department of Obstetrics and Gynecology, Tepecik Education and Research Hospital, and approval was obtained from the institutional ethics committee. The medical records of patients with tubal EP between January 2009 and September 2014 were reviewed retrospectively.

At our hospital, the treatment of patients pre-diagnosed with EP is guided by a treatment protocol in which hemodynamically stable patients are monitored with serial β-hCG measurements and ultrasonography. Patients with a $>$ 15% daily decrease in serial β-hCG measurements are regarded as having spontaneously resorbing EP and monitored expectantly. Hemodynamically unstable patients with positive embryonic cardiac activity and those with signs of intra-abdominal bleeding, such as pain, undergo surgery. Patients with an inadequate increase or $<$ 15% decrease in serial β-hCG measurements are regarded as progressive EP, and endometrial curettage is performed. After endometrial curettage, daily serial β-hCG measurements are continued, and methotrexate is given to patients in whom β-hCG levels plateau (daily decrease $<$ 15%) or increase. Patients with a contraindication for methotrexate treatment (abnormal liver or kidney function tests, presence of intrauterine pregnancy, active pulmonary disease, peptic ulcer, or presence of hematological or immunological disorder) and those who request surgery undergo elective surgery.

Methotrexate treatment is tailored according to the single-dose protocol (50 mg/m^2) and administered intramuscularly after calculating the body surface area. The day of administration is regarded as Day 1, and the serum β-hCG levels are determined on Day 4 and Day 7. Patients with a $>$ 15% decrease in the β-hCG level between Day 4 and Day 7 are considered to have responded to medical therapy, and β-hCG levels are measured weekly until they fall below 5 mIU/mL. Patients who do not show a $>$ 15% decrease in β-hCG levels between Day 4 and Day 7 and whose levels plateau or increase are administered an additional dose of methotrexate (50 mg/m^2) intramuscularly. Patients with an increase in serum β-hCG levels, despite two doses of methotrexate, and those with hemodynamic instability or severe abdominal pain undergo surgery, which is regarded as indicating medical treatment failure. This study evaluated patients who were diagnosed with progressive EP according to the above-mentioned protocol and who received methotrexate. The patients in the study were divided into success and failure groups and were compared in terms of age, gravida, parity, size of EP, β-hCG levels at Day 1, Day 4, and Day 7, and the need for an additional methotrexate dose.

IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) and MedCalc 14 software packages (https://www.medcalc.org/) were used in the analysis of the study data. The continuous variables were expressed mean ± standard deviation, median (q1 – q3), and the categorical variables were expressed as percentage. The Shapiro-Wilk test was used to determine if the variables were normally distributed. The independent-sample *t* test was used in the comparison of the two groups that showed normal distributions. The Mann–Whitney *U* test was used to compare the two groups that did not show normal distributions. Receiver operating characteristic (ROC) analysis was used to determine the appropriate cut-off values for independent markers and calculate sensitivity and specificity. The level of statistical significance was established at $p < 0.05$.

Results

The study enrolled 394 patients who were admitted with a prediagnosis of PTEP, and whose diagnosis was confirmed histopathologically by endometrial curettage. As per our clinical protocol, 335 of the 394 patients who were deemed eligible for methotrexate therapy were monitored until the β-hCG levels returned to normal; this group was regarded as the success group. The remaining 59 patients underwent surgery for severe abdominal pain, acute abdomen, or hematological instability and were regarded as the failure group (Figure 1). There were no significant differences between the success and failure groups in terms of demographic and clinical characteristics (Table 1).

The β-hCG levels on day 1 were significantly lower in the patients who responded to medical treatment (2116 ± 3157 mIU/mL vs. 4178 ± 3422 mIU/mL, $p < 0.0001$). Significant differences were also seen in the mean β-hCG value between the success and failure groups at Day 4 ($p = 0.0001$) and Day 7 ($p = 0.0001$; Table 2).

ROC analysis was used to identify a specific cut-off for the maximum success rate based on these levels. ROC analyses of the Day 1 β-hCG levels revealed that the optimum cut-off point for the β-hCG level was 1418 mIU/mL (area under ROC curve = 0.738; sensitivity = 83.1%,

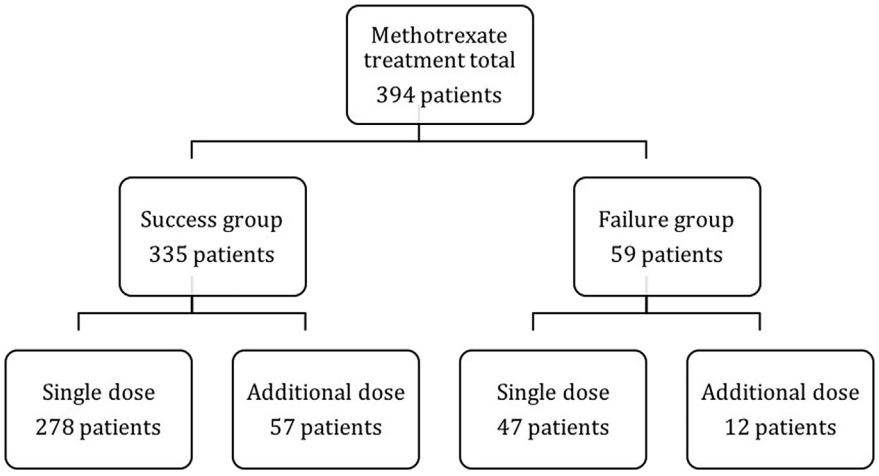

Figure 1. Flow chart of patients treated with single-dose methotrexate protocol.

Table 1 Characteristics of 394 women treated with methotrexate.

Characteristics	Methotrexate success ($n = 335$)	Methotrexate failure ($n = 59$)	p
Age (y)	30.44 ± 5.8 31.00 (26.00–34.00)	29.8 ± 5.3 30.00 (27.00–33.00)	0.468*
Parity (n)	1.03 ± 0.92 1.00 (0.00–2.00)	1.28 ± 1.21 1.00 (0.00–2.00)	0.64**
Gravidity (n)	2.57 ± 1.34 2.00 (2.00–3.00)	2.84 ± 1.34 3.00 (2.00–4.00)	0.144**
EU*** mass size, (mm)	19.6 ± 12.8 15.00 (10.00–25.00)	22.12 ± 14.5 17.00 (11.00–30.00)	0.185**

* Independent t test.
** Mann–Whitney U test.
*** Ectopic pregnancy.
Data are presented as mean ± SD and median (q1–q3).
EU = extrauterine; SD = standard deviation.

Table 2 β-hCG levels in success and failure groups on Day 1, Day 4, Day 7, and Day 11.

	Methotrexate success, mean ± SD, [median (q1–q3)]	n	Methotrexate failure, mean ± SD, [median (q1–q3)]	n	p
Day 1	2116 ± 3157 1333 (535–3857)	335	4178 ± 3422 2532 (498–4643)	59	<0.0001*
Day 4	2062 ± 3551 1779 (616–5615)	335	4935 ± 4103 3361 (624–6447)	47	<0.0001*
Day 7	1532 ± 3007 1566 (533–5032)	335	3900 ± 4783 2941 (555–7552)	31	<0.0001*
Day 11	2130 ± 3958 902 (294–3108)	58	1813 ± 2751 499 (123–2246)	12	0.793*

***** Mann–Whitney U test.
β-hCG = beta-human chorionic gonadotropin; SD = standard deviation.

specificity = 59.4%, percentage correctly classified = 95%). All of these parameters suggested good predictive accuracy for this cut-off. For clinical practice, a cut-off value of < 1418 mIU/mL β-hCG on Day 1 can be considered a good predictor of successful medical management with methotrexate (Figure 2). Table 3 shows the success rates and corresponding β-hCG values.

The examination of factors predicting the success of medical treatment showed a 6.86% increase in β-hCG levels between Day 1 and Day 4 associated with an 8.3-fold increase in the probability of treatment failure, with 69.58% sensitivity and 78.72% specificity.

Of the 394 patients in this study, 325 (82.48%) received single-dose methotrexate, and 69 patients (17.5%) required

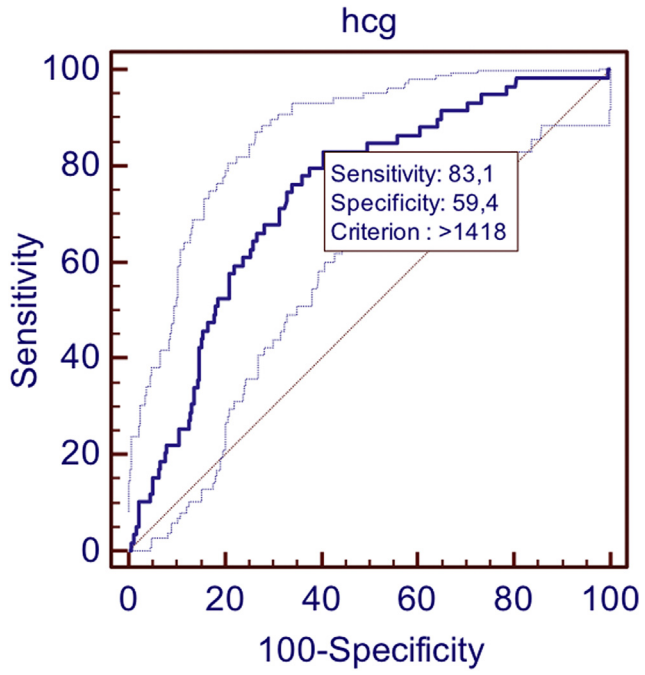

Figure 2. Receiver operating characteristic curve for Day 1 β-hCG levels following a single dose of methotrexate.

Table 3 Success rates for methotrexate according to β-hCG level.

β-hCG level (mIU/mL)	Cases (*n*)	Failures (*n*)	Success rate (%)
0–500	126	6	95.23
500–1000	59	4	93.22
1000–1500	29	2	93.10
1500–2000	33	5	84.84
2000–2500	23	5	78.26
2500–3500	32	7	78.12
3500–4500	20	7	65
> 4500	72	23	68.05
Total	394	59	85.02

β-hCG = beta-human chorionic gonadotropin.

an additional methotrexate dose. A comparison of these two groups found no significant differences in age, gravida, parity, or initial β-hCG levels (Table 4). There was a 7.93-fold increase in the need for an additional methotrexate dose, with 82.61% sensitivity and 75.81% specificity when the increase in β-hCG levels from Day 1 to Day 4 predicting the need for additional methotrexate dose was 8.25%. When the mean decrease in the β-hCG level from Day 1 to Day 4 was 9.87%, a 5.65-fold decrease was observed in the need for an additional methotrexate dose, with 77.7% sensitivity and 82.9% specificity ($p < 0.001$).

Of the 335 patients who responded to medical treatment, 57 received an additional methotrexate dose, and 12 of 59 in the failure group (all had tubal rupture) received an additional methotrexate dose. The mean age and gravida did not differ significantly between these patient groups,

Table 4 Characteristics and β-hCG levels of the patients treated with single- and additional dose methotrexate.

	Single dose	*n*	Additional dose	*n*	*p**
Age (y)	30.3 ± 5.7	325	30.5 ± 5.8	69	0.746
Gravida	2.6 ± 1.3	325	2.6 ± 1.3	69	0.836
Parity	1.07 ± 0.98	325	1.07 ± 0.92	69	0.990
Day 1 β-hCG	2374 ± 3201	325	2661 ± 3631	69	0.509
Day 4 β-hCG	2122 ± 3164	313	3748 ± 5496	69	0.001
Day 7 β-hCG	1339 ± 2558	297	3425 ± 4980	69	<0.001
Days 1–4 β-hCG (%)	−11.02 ± 42.5	312	36.43 ± 35.05	69	<0.001
Days 4–7 β-hCG (%)	−39.27 ± 25.3	294	−9.08 ± 17	69	<0.001
Days 1–7 β-hCG (%)	−44.20 ± 40.3	288	24.16 ± 40.2	69	<0.001

Data are presented as mean ± SD.
* Mann–Whitney *U* test.
β-hCG = beta-human chorionic gonadotropin; SD = standard deviation.

and there were no significant differences between the groups in terms of the β-hCG level at baseline, at Day 4, or in comparisons of Day 1 and Day 4, Day 4 and Day 7, and Day 7 and Day 11 (Table 5).

Discussion

With advances in imaging technology, EP is being detected earlier in pregnancy. With the introduction of methotrexate into clinical practice, surgical treatment has been mostly replaced by medical treatment. Treatment protocols that were approved ~2 decades ago are still effective [4]. In an article published by the American Society for Reproductive Medicine in 2013, hemodynamic instability (findings of tubal rupture) and severe abdominal pain increasing in

Table 5 Characteristics and β-hCG levels of the patients treated by additional methotrexate dose.

Additional methotrexate dose	Success group (*n* = 57)	Failure group (*n* = 12)	*p**
Age (y)	30.8 ± 6	28.9 ± 5	0.257
Gravida	2.59 ± 1.46	2.83 ± 1.02	0.356
Day 1 β-hCG	2525 ± 3697	3309 ± 3372	0.429
Day 4 β-hCG	3602 ± 5676	4442 ± 4697	0.393
Day 7 β-hCG	3280 ± 5097	4113 ± 4519	0.429
Days 1–4 β-hCG change (%)	36.8 ± 37.2	34.5 ± 23.2	0.975
Days 4–7 β-hCG change (%)	−8.3 ± 16.3	−12.65 ± 20	0.438
Days 7–11 β-hCG change (%)	−37.1 ± 28	−32.7 ± 24	0.590

Data are presented as mean ± SD.
* Mann–Whitney *U* test.
β-hCG = beta-human chorionic gonadotropin; SD = standard deviation.

severity, regardless of any change in β-hCG levels, and a $>$ 53% increase in β-hCG levels after the second dose in single-dose regimens and after the fourth dose in multiple-dosing regimens are regarded as indicators of a poor response to medical treatment [5].

Of the study patients, all of whom had PTEP, 59 underwent surgery for tubal rupture, and 335 patients were treated without requiring surgical intervention, for a success rate of 85.02%. Levin et al. [6] monitored asymptomatic patients with plateauing β-hCG levels and a prediagnosis of tubal EP for up to 5 days (mean, 2.65 days) to rule out spontaneously resorbing EP and to determine the true efficiency of methotrexate therapy in PT pregnancies. They administered methotrexate to patients with plateauing or sustained increases in β-hCG levels, referring to this approach as "watchful waiting" and reporting an 87% success rate for methotrexate treatment [6,7]. Sagiv et al. [8] reported success rates for methotrexate treatment in patients with asymptomatic tubal EP of 88% if β-hCG was $\leq$ 1000 mIU/mL and 71% if β-hCG was between 1000 mIU/mL and 2000 mIU/mL. They also reported tubal rupture in all members of the failure group, similar to the case in our study [8].

In this study, the mean initial β-hCG level was significantly lower in the success group (2116 $\pm$ 3157 mIU/mL) as compared with the failure group (4178 $\pm$ 3422 mIU/mL). The analysis performed to evaluate which β-hCG level was associated with a decrease in the efficiency of medical therapy indicated a cut-off value of 1418 mIU/mL, with 83.1% sensitivity and 59.4% specificity. When the success rate was evaluated according to the range of β-hCG values, the success rate declined from 90% to 80% for the cut-off value determined in the analysis (Table 3). Additionally, β-hCG values at Day 4 and Day 7 were lower in the success group. Many studies evaluated biochemical and sonographic parameters to determine predictors of the efficiency of medical therapy in patients with EP [9,10]. Yildirim et al. [11] found that an initial β-hCG level of 2000 mIU/mL predicted the response to treatment, and that values above this cut-off point were associated with a decreased success rate. Similarly, Menon et al. [12] reviewed the results of 500 patients in five studies and reported a cut-off value of 5000 mIU/mL, and suggested that medical treatment administered to patients with higher values was more likely to be associated with treatment failure. Nowak-Markwitz et al. [13] suggested a more precise cut-off value and reported a higher failure rate at $>$ 1790 mIU/mL, while Helmy et al. [14] reported a cut-off value of 2121 mIU/mL. Natale et al. [15] suggested that changes in β-hCG levels reflected differences in folinic acid metabolism across individuals. Additionally, methotrexate administration caused mitotic arrest in cytotrophoblasts, but β-hCG production was maintained in syncytiotrophoblasts. The authors concluded that β-hCG values at the initial dose and after methotrexate administration did not change significantly in the first few days [15].

Patient management based on the changes in β-hCG values at Day 4 and Day 7 after methotrexate therapy requires prolonged in-hospital patient monitoring. This approach not only causes patient anxiety, but also increases the treatment cost per patient. A reduction in this period would decrease the costs and avoid anxiety. Therefore, the efficacy of serial β-hCG measurements at Day 1 and Day 4 for predicting treatment success has long been studied. Agostini et al. [16] reported that a 20% decrease in β-hCG level predicted treatment success with a 97% positive-predictive value. Similarly, Ustunyurt et al. [17] reported that a 22% decrease in β-hCG level predicted treatment success. Celik et al. [18] studied 93 patients and reported a 4.94-fold increase in treatment failure associated with at least a 9.08% decrease in β-hCG levels from Day 1 to Day 4. Following methotrexate administration, a slight increase in β-hCG levels is usually expected in the first few days [18]. In our study group, ROC and logistic regression analysis of the change in β-hCG levels from Day 1 to Day 4 showed that a $>$ 6.86% increase in β-hCG level was associated with an 8.3-fold increase in the probability of treatment failure, with 69.58% sensitivity and 78.7% specificity. The decrease in β-hCG levels did not significantly predict treatment success ($p = 0.83$). Following the initial dose of methotrexate therapy, the need for an additional methotrexate dose is another factor causing patient anxiety and increased length of hospital stay. In our series, 69 patients (17.5%) required an additional methotrexate dose. The intragroup analysis of patients who received an additional methotrexate dose showed no significant difference between the success and failure groups in terms of initial β-hCG levels; therefore, a cut-off value could not be determined to predict treatment success. Cohen et al. [19] investigated the factors affecting treatment success in patients requiring an additional methotrexate dose, and unlike our results, they reported a significant difference between the initial β-hCG values of the success and failure groups and suggested that the success rate of an additional methotrexate dose was lower if the cut-off value was 2234 mIU/mL.

In this study, when patients who received methotrexate therapy were divided into single-dose and additional dose groups, regardless of the success rate, there was no significant difference between the two groups in terms of the initial β-hCG values. However, in the additional dose group, a $>$ 8.2% increase in β-hCG levels from Day 1 to Day 4 was associated with a 7.93-fold increase in the probability of receiving an additional dose (sensitivity 82.61%, specificity 75.81%, $p = 0.0017$). A 9.87% decrease in β-hCG levels from Day 1 to Day 4 was associated with a 5.65-fold decrease in risk. In a study of 88 patients, Atkinson et al. [20] emphasized that a decrease in the β-hCG level from Day 4 to Day 7 was superior to a decrease from Day 1 to Day 4 at predicting the need for an additional methotrexate dose. We did not make such a comparison, but instead evaluated the usefulness of changes from Day 1 to Day 4 for predicting the need for an additional methotrexate dose. Although the percentage changes found in our study were not sufficiently high to be used in daily practice, these findings were beneficial from the perspective of providing insight into the need for additional doses.

In conclusion, with one of the largest reported patient series, our study suggested a higher success rate in patients with PTEP and lower initial β-hCG levels, and the chance of success was lower above a dose cut-off value of 1418 mIU/mL. Additionally, the chance of success and the need for additional methotrexate doses could be predicted based on changes in β-hCG from Day 1 to Day 4.

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